REMARKS

Applicant respectfully requests entry of the amendments and remarks submitted herein. Claims 29-30 are amended, and claims 1-28, 31-53 and 59-63 are canceled. Therefore, claims 29-30 and 54-58 are currently pending.

Certain specific long-circulating liposomes have been studied in human clinical trials. Specification at page 2, lines 9-16. A significant problem with such long-circulating liposomes, however, results from an inability to properly balance the enhanced circulation lifetime of the liposomes with specific drug release profiles. Although investigators have successfully increased the circulation lifetimes of drugs encapsulated in pegylated liposomes, which beneficially promotes accumulation of the liposomes at tumor growth sites, they have been unable to realize acceptable drug release profiles from these liposomes for certain therapeutic agents. Specification at page 2, lines 23-29.

A liposomal system was needed that was generally useful for improving the therapeutic index and activity of non-amphiphilic therapeutic agents. Specification at page 3, lines 17-19. Applicant has developed such a system, *i.e.*, a liposomal system that provides intermediate elimination half-lives for lipophobic therapeutic agents. These intermediate elimination half-lives are longer than the elimination half-lives of the free therapeutic agent (*i.e.*, the agent administered in the absence of the liposomes). Thus, the liposome systems recited in the instant claims typically improve the therapeutic index and the activity of the lipophobic agents. Additionally, the drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously studied long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release encountered in earlier long circulating liposomes. Specification at page 2, lines 28-29.

Accordingly, the liposome systems recited in the instant claims improve the therapeutic index and the activity for the lipophobic agents, while still providing adequate release of the lipophobic agents. No prior liposome system provided this combination of properties for lipophobic therapeutic agents.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 24-30 and 39-58 under 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-28 and 39-53 have been cancelled. Claims 54-58 recite formulations comprising a lipophobic therapeutic agent encapsulated in specific liposomes. Claims 29 and 30 have been amended to depend from any one of claims 54-58.

This rejection is respectively traversed with respect to claims 54-58. Page 2-3 of the Office Action states that the independent claims recite "two functional limitations 1 and 2, which contradict each other in terms of half-life." Applicant respectfully asserts that none of the pending claims recite language regarding half-life of the therapeutic agent. Accordingly, Applicant requests the withdrawal of the rejection of claims 29-30 and 54-58.

Rejections under 35 U.S.C. § 103(a)

1. Claims 24-30 and 39-63 – Hersch, Allen, Fijii and O'Rear

The Examiner has rejected claims 24-30 and 39-63 under 35 U.S.C. §103(a) as being unpatentable over Hersch (5,759,571) by itself or in combination with Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination. This rejection is respectfully traversed.

Claims 24-28, 39-53 and 59-63 have been cancelled.

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the framework for the objective analysis of determining obviousness under 35 U.S.C. § 103(a) is stated in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The factual analysis involves (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claims at issue, and (3) resolving the level of ordinary skill in the pertinent art. Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, often called "secondary considerations," include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. Cited documents must be considered in their entirety, and it is not permissible to pick and choose from any one document only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such document fairly suggests to one of

ordinary skill in the art (*see, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986) and *In re Wesslau*, 353 F.2d 238, U.S.P.Q. 391 (C.C.P.A. 1965)).

Claim 54 recites formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1. Claims 29-30 depend from claim 54. Hersch at col. 6, lines 11-17 recites liposomes with a preferred ratio of HSPC:cholesterol:DSPG of about 2:1:0.1 and that "[o]ther preferred formulations include DSPG in a molar amount of 0 to 20% and most preferably in a molar amount of less than 5%." The Office Action has provided no text reference or knowledge why the 2:1:0.1 HSPC:cholesterol:DSPG ratio mentioned by Hersch teaches the ratio of 4:1:0.1 (*i.e.*, where the amount of HSPC is double of that taught by Hersch) as recited in claim 54. Even if Hersch discusses that the amount of DSPG may vary, there is no teaching or suggestion that the amount of HSPC:cholesterol is 4:1. Thus, Hersch does not teach all of the features of claims 29-30 and 54.

Further, the Hersch formula of 2:1:0.1 HSPC:Chol:DSPG would have a very long half life as compared to the presently claimed ratio that has an intermediate release value, which imparts an unexpected result to the present claims as compared to what is taught by Hersch. As discussed above, the Applicant's system provided a needed balance between elimination half-life times that were too short or were too long. Applicant's system provides intermediate elimination half-lives for lipophobic therapeutic agents. The drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously studied long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release of previously-known liposomes.

Claim 55 recites a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1. Claims 29-30 depend from claim 55. Hersch does not teach or suggest a formulation of DEPC:Cholesterol. Thus, Hersch does not teach all of the features of claims 29-30 and 55.

Claim 56 a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1. Claims 29-30 depend from claim 56. Hersch does not teach or suggest a formulation of DEPC:Cholesterol:DSPG. Thus, Hersch does not teach all of the features of claims 29-30 and 56.

Claim 57 recites a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1. Claims 29-30 depend from claim 57. Hersch does not teach or suggest a formulation of DOPC:Cholesterol. Thus, Hersch does not teach all of the features of claims 29-30 and 57.

Claim 58 recites a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1. Claims 29-30 depend from claim 58. Hersch does not teach or suggest a formulation of DMPC:Cholesterol in a ratio of about 2:1:0.1. Thus, Hersch does not teach all of the features of claims 29-30 and 58.

As characterized by the Examiner, the Allen, Fujii and O'Rear references discuss liposomes that include cholesterol. However, these citations do not speak to the difference between the ratios of phosphatidylglycerol lipids to phosphatidylcholine lipids as discussed above and thus do not remedy the deficiencies of Hersch. These references all utilize different liposomal constituents and result in significantly different liposomes. The liposomes of Allen are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54, DEPC:Cholesterol as recited in claim 55, DEPC:Cholesterol:DSPG as recited in claim 56, DOPC:Cholesterol as recited in claim 57, or DMPC:Cholesterol:DSPG as recited in claim 58. Instead, Allen used egg phosphatidylcholine (egg lecithin), dipalmitoylphosphatidylcholine (DPPC) or distearoylphosphatidylcholine (DSPC), none of which are recited by the present claims. Allen at page 420. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54, DEPC:Cholesterol as recited in claim 55, DEPC:Cholesterol:DSPG as recited in claim 56, DOPC:Cholesterol as recited in claim 57, or DMPC:Cholesterol:DSPG as recited in claim 58. Instead, O'Rear used 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC), which is not recited by the present claims. O'Rear at col. 5, line 51. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

Lastly, the liposomes of Fujii are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54, DEPC:Cholesterol as recited in claim 55, DEPC:Cholesterol:DSPG as recited in claim 56, DOPC:Cholesterol as recited in claim 57, or DMPC:Cholesterol:DSPG as recited in claim 58. Instead, Fujii used distearoylphosphatidylcholine (DSPC) and cholesterol, which is not recited by the present claims. Fujii at col. 3, lines 1-12 and 46-48 and col. 4, lines 31-32. The liposomes of Fujii are highly stable and thus are slow release liposomes, whereas the liposomes of the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

Accordingly, the Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the liposomes recited in the instant claims. Therefore, the withdrawal of the rejection of claims 29-30 and 54-58 is respectfully requested.

2. Claims 24-30 and 39-63 – Lopez-Berestein, Allen, Fujii, O'Rear and Hersch

The Examiner has rejected claims 24-30 and 39-63 under 35 U.S.C. §103(a) as being unpatentable over Lopez-Berestein (5,032,404) by itself or in combination with Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination, further in view of Hersch (5,759,571). Page 2 of the Office Action states that the rejection under 35 U.S.C. §103(a) of claims 24-30 and 39-63 over Lopez-Berestein by itself or in combination with Allen, Fujii and O'Rear is withdrawn. Applicant presumes, therefore, that the Examiner intended that the present rejection be over Lopez-Berestein in combination with Allen, Fujii, O'Rear and Hersch.

Claims 24-28, 39-53 and 59-63 have been cancelled. This rejection is respectfully traversed with respect to claims 54-58.

Lopez-Berestein describes a system wherein a hydrophobic therapeutic agent is trapped in the lipid bilayer of the liposome, rather than being located in the hydrophilic interior of the liposome. In contrast, the instant claims recite a lipophobic (*i.e.*, a hydrophilic) therapeutic agent. The specification at page 8 recites:

> The term "lipophobic therapeutic agent" includes compounds that are water soluble enough to achieve a useful level of loading by passive encapsulation and that are significantly impermeable once loaded. The term excludes agents that are both amphiphilic and that can be effectively gradient loaded into liposomes.

Accordingly, the formulations of the invention are typically prepared by passive loading of liposomes.

Further, Lopez-Berestein teaches away from the recitations of the rejected claims. The liposomes of Lopez-Berestein are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54, DEPC:Cholesterol as recited in claim 55, DEPC:Cholesterol:DSPG as recited in claim 56, DOPC:Cholesterol as recited in claim 57, or DMPC:Cholesterol:DSPG as recited in claim 58. In contrast, Lopez-Berestein discusses "DMPG" while failing to discuss "DSPG." Moreover, Lopez-Berestein at column 8, lines 4-7 discusses liposomes comprising dimyristoyl phosphatdylglcerol (DMPG) and dimyristol phosphatidylcholine (DMPC) in ratios of about 1:10 and 10:1 and more preferably in a ratio of about 3:7. Thus, claims 54-57 recite different specific lipids as compared to those taught by Lopez-Berestein, and the ratio of phosphatidylglycerol lipids to phosphatidylcholine lipids in all of the pending claims is significantly different even when comparing the most similar ratios (40:1 versus 10:1). The Examiner has not provided any scientific reasoning why one would be led to a ratio of 40:1 from the Lopez-Berestein ratio of 10:1. Accordingly, claims 54-58 would not be obvious when the art teaches a ratio of about 10:1. Claims 29-30 depend from claims 54-58 and therefore are also not obvious.

Allen, Fujii, O'Rear, and Hersch neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulations or ratios of phospholipids and cholesterol to form the liposomes recited in the instant claims, the withdrawal of the rejection of claims 29-30 and 54-58 is respectfully requested.

3. Claims 29 and 44-48 – Lopez-Berestein, Allen, Fujii, O'Rear and Hersch OR Hersch, Allen, Fujii, O'Rear and Abra

The Examiner has rejected claims 29 and 44-48 under 35 U.S.C. §103(a) as being unpatentable over Lopez-Berestein, Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination and Hersch; OR Hersch, Allen (BBA), Fujii (5,328,678), O'Rear

(5,503,850) individually or in combination also as set forth above, further in view of Abra (5,945,122).

Claims 44-48 have been cancelled, and claim 29 has been amended to depend from claims 54-58. This rejection therefore is now moot.

4. Claims 25-26, 28, 40, 41, 43, 55-56, 58-61 and 63 – Hays, Hersch, Allen Fujii and O'Rear

The Examiner has rejected claims 25-26, 28, 40, 41, 43, 55-56, 58-61 and 63 under 35 U.S.C. §103(a) as being unpatentable over Hays (5,869,092) by itself or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination.

Claims 25-26, 28, 40, 41, 43, 59-61 and 63 have been cancelled.

Pending claims 55-56 and 58 are described in detail above.

This rejection is respectfully traversed. Hays describe liposome systems that are very different than the liposomes recited in the instant claims. Hays discusses the use of DPPC, egg phosphatidylethanolamine, DEPC and DMPC (col. 9, lines 35-38), and specifically made liposomes from DEPC (Example 1). Hays states that a sterol such as cholesterol may be present, and when a sterol such as cholesterol is present, the mole ratio of sterol to phospholipid is generally from about 0.1:1.0 (col. 8, lines 4-6). This ratio differs significantly from the ratio recited in the present claims, which has a sterol:phospholipid ratio of 4:1 or 2:1. This structural difference imparts a significant functional distinction to the presently claimed invention. The liposomes described by Hays would not have intermediate release properties. Although Hays describes a liposome comprising DEPC and mentions in a broad manner that cholesterol may be present, no guidance is provided relative to the amounts of cholesterol that would lead to a liposome with intermediate release of a lipophobic agent. Although Hays mentions negatively charged phospholipids, Hays does not suggest or teach either the lipids recited in instant claims or the ratios of the lipids to one another. The proper selection of both of these elements provides for liposomes that have intermediate release properties consistent with the functional element of the claims.

The cited references Allen, Fujii and O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes such as

those described in the rejected claims. Furthermore, Hersch does not teach or suggest the compositions or ratios of the formulations of claims 55-56 and 58. Therefore, there is no explicit or inherent reason to combine the cited references to arrive at the liposomes of the rejected claims.

Accordingly, the Hays, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the liposomes recited in the instant claims. Therefore, the withdrawal of the rejection of claims 55-56 and 58 is respectfully requested.

5. Claims 27, 42, 47, 52, 57 and 62 – Hayes, Hersch, Allen, Fujii, O'Rear and Anaissie

The Examiner has also rejected claims 27, 42, 47, 52, 57 and 62 under 35 U.S.C. §103(a) as being unpatentable over Hayes (5,869,092) alone or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination as set forth above, further in view of Anaissie (4,999,199).

Claims 27, 42, 47, 52 and 62 have been cancelled.

Pending claim 57 recites a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1.

This rejection is respectfully traversed. Claim 57 is not obvious over Hays alone or in combination with Hersch, Fujii, or O'Rear for reasons similar to those discussed above. Hays does not discuss a liposome that comprises DOPC:Cholesterol, and does not discuss a formulation of DOPC:Cholesterol in a ratio of about 2:1. Fujii, O'Rear, and Hersch neither individually nor in combination with Hays remedy the deficiencies of Hays because none of these references teach or suggest all the features of the present claimed invention. As discussed above, the presently claimed liposomes are different structurally and are functionally distinguishable over those discussed by Hays, Hersch, Allen, Fujii, and O'Rear.

Anaissie discusses the preparation of liposomes that are stable multilamellar vesicles that comprises phospholipids and may include a sterol such as cholesterol (col.3, lines 48-64). In particular, Anaissie discusses the use of the lipids Egg phosphatidylcholine (EggPC), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG) dielaidoylphosphatidylcholine (DEPC) phosphatidylthanolamine (PE), dioleolylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC),

dipalmitoylphosphatidylcholine (DPPC) and cholesterol (col. 7, lines 19-28). Anaissie, however, does not teach or suggest the formulation of DOPC:Cholesterol in a ratio of about 2:1, as recited by claim 57. Anaissie, only mentions the mixture of EggPC/cholesterol at a ratio of 9:1, the mixture of DMPC/DMPG at a ratio of 7:3, and mixtures of DPPC/PE/cholesterol, or DSPC/PE/cholesterol, or DEPC/PE/cholesterol in a ratio of 6.5:2.5:1 and to DOPC/PE/cholesterol in a ratio of 6:3:1.

Accordingly, the Hays, Hersch, Allen, Fujii, O'Rear and Anaissie references when taken singly or in combination do not teach or suggest the all of the features of the liposomes recited in the instant claims. Therefore, the withdrawal of the rejection of claim 57 is respectfully requested.

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

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